Plasmanate®

A New Plasma Substitute for Pediatric Therapy

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• **Plasmanate®, a human-serum protein solution, appears to have all the attributes of an ideal plasma expander. Freedom from infection, immediate availability in a clear, stable solution and the apparent absence of antigenic properties are particularly valuable qualities. The efficacy and safety of Plasmanate was clinically demonstrated in the treatment of 125 infants and children. This solution seems especially effective in the treatment of acute shock states and for the physiologic correction of hypoproteinemia. Comparison with other plasma expanders makes Plasmanate the agent of choice in the initial treatment of shock states in pediatrics.**

THIS REPORT describes a two-year experience in which 125 infants and children have received intravenous infusions of a fractionated, human-serum, protein solution, Plasmanate.®* This solution has the attributes of an ideal plasma substitute: (1) Immediate availability in a clear, free-flowing, stable solution, (2) freedom from infectious agents, pyrogens, toxins, and antigens, (3) a virtually potassium-free, electrolytically hypotonic solution, (4) oncotic activity equivalent to plasma, and (5) physiologic protein material.

Fundamental objectives of this study were the development of clinical indications and the evaluation of efficacy and safety of this unique solution.

PROPERTIES OF PLASMANATE

The proteins of Plasmanate (albumin, alpha-globulin, and beta-globulin) are obtained as by-products during the Cohn fractionation of human serum in the process of recovering gamma-globulin and fibrinogen. When reconstituted as a 5 per cent solution in a diluent of 0.75 per cent saline at a pH of 6.75 to 7.25, the proteins show an electrophoretic composition of 88 per cent albumin, 7 per cent alpha-globulin, and 5 per cent beta-globulin (Table 1). The oncotic activity is comparable to that of plasma. The solution is virtually potassium-free and is hypotonic electrolytically. All the essential amino acids are present in the protein fraction. The possibility of transmitting the virus of homologous serum hepatitis has been eliminated by heating at 60° C. for 11¼ hours. (Gellis[4] in 1948 and Murray[7] in 1953 demonstrated that this virus is completely destroyed by heating at 60° C. for ten hours.) The proteins of Plasmanate are heat-stable and show no evidence of alteration by the heat treatment.[6] Plasmanate is a crystal-clear, amber solution that appears to be infinitely stable at shelf temperature.

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CLINICAL STUDIES

Two groups of children were studied clinically. In one were 94 acutely ill infants and children in extreme shock states associated with the dehydration of diarrhea, toxemia and infections, and with extensive burns. In the other were 26 chronically ill children who had pronounced serum protein deficiencies due to such causes as idiopathic hypoproteinemia, malnutrition and burns. All children were observed for any reactions, complications or problems that might be associated with the infusion of human-serum proteins.

Plasmanate was used in the following dosage schedule:

In acute shock states (as plasma expander): 30 cc. per kilogram (15 cc. per pound) of body weight, infused intravenously at up to 5 to 10 cc. per minute.

TABLE 1.—*Electrophoretically Determined Content of Human Serum Protein Solution, Plasmanate®*

1. 88 per cent albumin, 7 per cent alpha globulin and 5 per cent beta globulin, including all essential amino acids.
2. Electrolytes per liter:

Sodium	111 mEq.
Calcium	1.6 mEq.
Magnesium	0.8 mEq.
Potassium	0.5 mEq.
Silicon	0.2 mEq.
Chloride	61 mEq.
Caprylate	4 mEq.
Acetyl-tryptophane	4 mEq.
Proteinate	36 mEq.
Acetate	6 mEq.

In chronic hypoproteinemia: 20 to 30 cc. per kilogram (10 to 15 cc. per pound) of body weight, infused daily, as required, by slow intravenous drip.

Among the patients in acute shock states there was rapid response as indicated by improved color, response to stimuli, improved orientation and restoration of normotensive blood pressure in 95 per cent (Table 2). Four infants who were considered to have a hopeless prognosis on admission responded to therapy with clinical improvement but died later of causes related to the primary illness.

TABLE 2.—*Response to Plasmanate in 94 Children in Acute Shock States*

Clinical Entity	Total Cases	Immediate Clinical Response	Sustained Clinical Response	Adverse Reaction
Gastroenteritis and dehydration	66	64	63	0
Peritonitis	3	3	3	0
Meningitis	3	2	2	0
Pneumonitis	3	3	3	0
Hemolytic disease of newborn	1	1	0	0
Blood loss at operation	4	4	0	0
Thermal burns	4	4	1	0
Acute poisoning	1	1	0	0
Hyaline membrane	1	1	0	0
Blood dyscrasias	2	2	0	0
Sicklemic crisis	6	4	2	0
Totals	94	89	74	0

TABLE 3.—*Response to Plasmanate in 26 Children in Hypoproteinemic States*

Clinical Entity	Total Cases	Clinical Improvement	Serum Protein Increase
Subdural hematomata	3	3	1
Thermal burns	4	2	1
Cachexia (malnutrition)	2	2	2
Postsurgical	8	6	1
Chronic gastroenteritis	6	6	3
Nephrosis	1	1	1
Idiopathic	2	2	2
Totals	26	22	11

Among the 26 children with persistent hypoproteinemia associated with thermal burns, subdural hematoma, malnutrition and chronic diarrhea, 22 responded to Plasmanate therapy with return of strength, gain in weight and satisfactory healing of surgical incisions and skin grafts (Table 3). Eleven had a significant increase in serum-protein content following repeated administration of Plasmanate.

More than 300 units of the solution were given to 125 infants and children in a period of two years. In no instance was there any evidence of sensitization, reaction or hepatitis, although 29 patients received repeated infusions at varying intervals (Table 4). Thirty-seven patients subsequently received whole-blood transfusions, and in no instance was there interference with type and cross-match procedure or with the transfusion.

DISCUSSION

One of the most urgent therapeutic emergencies encountered in pediatrics is the treatment of shock associated with the acute dehydration of diarrhea, toxemia or infection. An immediate need is to expand the circulating blood volume safely by the rapid infusion of a suitable plasma expander. All the agents that have been offered thus far as plasma expanders have serious deficiencies:

Plasma: The transmission of viral homologous-serum hepatitis has limited the use of this agent to only the most critical cases. Davidson[3] reported the incidence of hepatitis resulting from the use of pooled plasma to be 11.9 per cent. Shelf-stored plasma contains an opalescent gel with fibrin-like clots, which limits its immediate value as an intravenous preparation.[1] The content of sodium (156 mEq. per liter) and of potassium (5.2 mEq. per liter) is higher than desirable and would be dangerous to infuse into a dehydrated patient. The difficulty of quickly putting the lyphilized product into a solution limits its usefulness.

Serum albumin: This fraction has dehydrating properties that contraindicate its use in dehydrated infants. The rapid expansion of blood volume may

TABLE 4.—*Observation for Ill Effects of Plasmanate Infusion in 125 Children*

Number of Patients Receiving	Total	1 Month Between Administrations	1 to 6 Months Between Administrations	6 to 18 Months Between Administrations	Immediate Untoward Effects†	Subsequent Untoward Effects‡
1 unit* or less	96	....	....	....	0	0
2 to 4 units	19	16	2	1	0	0
5 to 10 units	3	1	1	1	0	0
More than 10 units	7	5	2	....	0	0
Totals	125	22	5	2	0	0

*1 unit contains 250 cc. Plasmanate.

†Observation for: Hyperpyrexia, hypotension, albuminuria, urticaria.

‡Observation for: Tissue damage, hepatitis, or interference with typing and cross-matching and transfusion procedures (37 of 125 patients were subsequently typed and cross-matched without interference or incident).

be accomplished at the expense of the fluid in an already depleted extravascular compartment. The development of hypervolemia with congestive heart failure or pulmonary edema following rapid infusion of serum albumin is a real hazard.

Amino acid solutions: Casein hydrolysates and other costly amino acid solutions are available. They are primarily designed to provide protein to the patient in negative nitrogen balance. Their value in shock is minimal, and they are contraindicated if anuria or azotemia is present.

Whole blood: In emergency situations, use of whole blood is limited by the time required for accurate typing and cross-matching, and by the immediate danger in transfusing it into a hemoconcentrated vascular bed. Fatal reactions occur in approximately 1 of 3000 transfusions[3] and hepatitis in 1 of 350 transfusions.[3] The long-range hazards of sensitization and immunization are infinite.

Bovine gelatin preparations: These are reported to interfere with typing and cross-matching procedures.[9] Most of them do not remain gels at body temperature. They stay in the circulatory system for a limited time, and it is estimated that approximately 60 per cent is lost through the kidneys in 24 hours. Hartmann[5] showed that gelatin, like other foreign substances, provokes formation of foam cells and foreign-body giant cells in the reticuloendothelial system.

Dextran® (6 per cent polysaccharide solution): Allergic reactions have been reported, and a Schwartzman-like reaction has been produced by repeated injection of Dextran into laboratory animals.[10] Recently Langdell[8] reported the appearance of a hemostatic defect characterized by prolonged bleeding time in 42 per cent of normal subjects who had been infused with Dextran.

Polyvinylpyrrolidone (PVP): This agent may produce cytotoxic changes in the nature of foam cells. Another disadvantage is the rapidity with which it is excreted from the body.[9]

Polyionic solutions: Commercial polyionic solutions containing potassium and varying quantities of electrolytes are dangerous when blindly infused in the face of poor renal function and abnormal serum content.

Plasmanate: The fractionated, human-serum, protein solution herein reported appears to answer many of the problems. Plasmanate provides most of the desirable attributes of plasma with none of the undesirable features. The oncotic activity, physiological pH, the hypotonic electrolyte content, and the presence of proteins that contain all the essential amino acids make Plasmanate a particularly attractive solution for initial intravenous therapy for an infant who is depleted by diarrheal disease. Infant diarrhea usually involves hemoconcentration (diminished blood volume), serum sodium deficiency, and surplus of serum chloride (hypochloremic acidosis) and potassium. Under such conditions, there is usually oliguria or anuria.

In the past, so-called physiological saline solution was often forced as the initial solution to combat shock and restore blood volume. In normal saline solution the chloride content is 155 mEq. per liter, whereas in the normal serum, chloride is only 103 mEq. per liter. The rapid injection of physiologic saline solution may add a proportionately large load of chloride to an already high serum level and already overburdened kidneys. Recently, Cheek[2] demonstrated that when high initial loads of sodium chloride were used, there was a prolongation of acidosis beyond 24 hours. Administration of low initial sodium chloride loads was associated with a more consistent reduction of acidosis at 24 hours and with return to normal serum chemical values at 72 hours. It seems logical to assume that Plasmanate, which has relatively more sodium (111 mEq. per liter) than chloride (61 mEq. per liter), osmotic pressure parallel to that of plasma, acidity within physiologic limits and negligible potassium content, would constitute an almost ideal solution for initial therapy in infants with acidosis, dehydration, and electrolyte depletion. The authors' experience indicates that this is the case.

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REFERENCES

1. Allen, J. G., et al.: Pooled plasma with little or no homologous serum jaundice, J.A.M.A., 154:103-106, Jan. 9, 1954.

2. Cheek, D. B.: Changes in total chloride and acid-base balance in gastroenteritis following treatment with large and small loads of sodium chloride, Pediatrics, 17:839-848, June, 1956.

3. Davidson, W. C.: Viral hepatitis and its risk from blood and plasma transfusions, J. of Pediat., 46:717-720, June 1955.

4. Gellis, S. S., et al.: Chemical, clinical and immunological studies on products of human plasma fractionation; inactivation of virus of homologous serum hepatitis in solutions of normal human serum albumin by means of heat, J. Clin. Invest., 27:239-244, March 1948.

5. Hartman, F. W., and Behrmann, V. G.: The present status of plasma expanders, J.A.M.A., 152:1116-1120, July 18, 1953.

6. Hink, J. H., et al.: Preparation and properties of a heat-treated human plasma protein fraction, Vox Sanguinis, 2:174, 1957.

7. Murray, R., and Diefenbach, W. C. L.: Effect of heat on the agent of homologous serum hepatitis, Proc. Soc. Exper. Biol. & Med., 83:554-555, July 1953.

8. Langdell, R., Adelson, E., Furth, F., and Crosby, W.: Dextran and prolonged bleeding time, J.A.M.A., 166:346-350, Jan. 25, 1958.

9. Ravdin, I. S.: Plasma expanders, J.A.M.A., 150:10-13, Sept. 6, 1952.

10. Thomas, L., Brunson, J., and Smith, R. T.: Studies on the generalized Schwartzman reaction. VI. Production of the reaction by the synergistic action of endotoxin with three synthetic acidic polymers (sodium polyethanol sulfonate, dextran sulfate, and sodium polyvinyl alcohol sulfonate), J. Exper. Med., 102:249-261, Sept. 1955.